Short interpregnancy intervals and risks for birth defects: support for the nutritional depletion hypothesis

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ABSTRACT

Background: Research suggests short interpregnancy intervals increase risks for adverse perinatal outcomes, including some birth defects. A hypothesized cause is nutritional depletion, including folic acid (FA).

Objectives: We evaluated associations between short interpregnancy intervals, alone and in combination with FA intake, and the occurrence of select malformations.

Methods: Data were from the National Birth Defects Prevention Study (US case–control, 1997–2011). Participants included multiparous women whose prior pregnancy resulted in live birth. Cases included 8 noncardiac and 6 cardiac defect groups ($n = 3219$); controls were nonmalformed live-borns ($n = 2508$). We categorized interpregnancy interval (<6, 6–11, 12–17, and 18–23 mo) and periconceptional FA intake [no FA supplement use and dietary folate equivalents (DFE) <400 μg/d, no FA supplement use and DFE ≥400 μg/d, or any FA supplement use]. We controlled for age, race/ethnicity, income, pregnancy intention, and study center. ORs <0.8 or >1.2 were considered to represent potentially meaningful associations.

Results: ORs for <6 compared with 18–23 mo were >1.2 for 4/8 noncardiac and 3/6 cardiac malformations. Among participants with any FA supplement use, ORs comparing <6 with 6–23 mo were <1.2 for most defects. Conversely, most ORs were >1.2 for <6 mo + no FA supplement use and DFE <400 μg/d compared with 6–23 mo + any FA supplement use. Magnitude and precision varied by defect.

Conclusions: Short interpregnancy intervals were associated with a trend of higher risks for several defects, notably in the absence of FA supplement use. To our knowledge, our study is the first to provide preliminary empirical support that these etiologies may be related to shorter interpregnancy intervals and possible nutritional deficiencies. Because FA intake is highly correlated with other nutrients, and because our estimates were generally imprecise, more research with larger sample sizes is needed to better understand the role of FA compared with other nutrients in each defect-specific etiology. *Am J Clin Nutr* 2021;113:1688–1699.

Keywords: birth defects, birth spacing, folic acid, interpregnancy interval, nutritional deficiency, pregnancy

Introduction

Interpregnancy interval is the time between the end of 1 pregnancy and the start of the next. Short interpregnancy intervals, typically defined as <6 mo, have been associated with complications and adverse outcomes of the subsequent pregnancy (1, 2), including some congenital malformations. The strongest associations have been observed with neural tube defects (NTDs) and gastroschisis, followed by cardiac and cleft defects (adjusted ORs: 2.1–1.4) (3–5). Short intervals have been associated with increased risks for NTDs and cardiac defects in more than 1 study (4, 6, 7).

Women with poorer nutrition and/or low folate may be particularly susceptible to adverse outcomes following short interpregnancy intervals (8, 9). Without the support of supplementation, the demands of pregnancy and lactation can result in reduced folate concentrations through 6 mo postpartum (10).

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Abbreviations: DFE, dietary folate equivalents; d-TGA, dextro-rotated transposition of the great arteries; FA, folic acid; HLHS, hypoplastic left heart syndrome; NBDPS, National Birth Defects Prevention Study; NTD, neural tube defect; PVS, pulmonary valve stenosis; VSD, ventricular septal defect.

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Research supports that when in a state of depletion, nutrients preferentially partition to the mother at the expense of the fetus (11). Furthermore, van Eijsden et al. (12) found that associations between short interpregnancy intervals and low birth weight were strongest among women who did not use folic acid (FA)–containing supplements, weaker among late pregnancy initiators, and absent among early initiators. FA is critical to fetal development (13, 14), protects against the occurrence of NTDs (15, 16), and has been associated with other birth defects (17–19) and other adverse pregnancy outcomes (20). To our knowledge, empirical evidence has yet to be provided to support the nutritional and/or folate depletion hypothesis in the relation between short interpregnancy intervals and increased risks for certain birth defects.

We sought to examine this hypothesis using data from the National Birth Defects Prevention Study (NBDPS). We evaluated associations with short intervals and FA intake separately as well as jointly (e.g., women exposed to both compared to neither). In an attempt to distinguish between the effects of FA and other nutrients, we considered FA intake from diet separately from vitamin supplementation. If short intervals increase defect risks in the presence of no supplement use, as observed in the study by van Eijsden et al. (12), these data could suggest that nutritional depletion may be a part of the biologic mechanism. Furthermore, stronger associations observed among women who also have low dietary folate intake could suggest that FA in particular may play an important role for certain etiologies.

Methods

The NBDPS was a US population-based case–control study that involved surveillance systems in Arkansas, California, Georgia, Iowa, Massachusetts, North Carolina, New Jersey, New York, Texas, and Utah to identify pregnancies affected by major, nonchromosomal birth defects (21). Cases included terminations, fetal losses, and live births. Clinical geneticists confirmed diagnoses; single-gene disorders and chromosomal abnormalities were excluded. Cases were classified according to the presence of various structural malformations. Controls were live-born infants with no major malformations who were randomly selected from birth certificates [Arkansas, Georgia (2001–2009), Iowa, Massachusetts, North Carolina, New Jersey, and Utah] and delivery records from the same hospitals as cases [California, Georgia (1998–2001), New York, and Texas]. Each center obtained study approval from its local institutional review board. To be eligible for the NBDPS, the estimated due date needed to be between October 1, 1997, and December 31, 2011. Among those eligible, consent rates were 67.4% and 64.8% for cases and controls, respectively. Within 2 y of delivery, participants completed a standardized telephone interview, which included questions on reproductive history, demographic characteristics, lifestyle and behaviors, and pregnancy. We conducted our analysis according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for case–control studies (22).

We defined interpregnancy interval as the time between the preceding delivery and the start of the study pregnancy. The estimated conception date was calculated as the estimated due date minus 266 d or, for participants missing an estimated due date, as the date of the last menstrual period plus 14 d. When the day was missing for the previous delivery date, we assigned the 15th of the month to compute interpregnancy interval (<0.3% of cases and controls); otherwise, we excluded women with missing dating information (6.8% cases and 5.6% controls). We converted the interval from days to months by dividing by 30.42 and categorized as <6, 6–11, 12–17, or 18–23 mo to be comparable to prior studies (3, 4, 6, 23); we excluded longer intervals because adverse outcomes may be due to a different etiologic mechanism.

In the interview, participants reported product, frequency, and dose of supplements (including multivitamins, prenatal vitamins, and those containing FA only) for the 3 mo before through the duration of pregnancy. These data were classified according to whether the reported supplements contained FA and the specific timing during pregnancy. The time period of interest for our analysis was the 28 d before through the first 56 d of the study pregnancy (herein referred to as "periconception") because most defects occur early in gestation. Most FA-containing supplements include other vitamins and minerals, although specific contents vary by product (24, 25). In our study, data were not available on other specific components. The NBDPS participants also completed a modified Willett FFQ (26), which included additional questions on cereal intake to improve FA quantification given fortification. The assessment summarized typical diet for the year before the study pregnancy, which we assumed would be similar to that of early pregnancy before recognition. Nutrient matrices were used to estimate average daily intake of macro- and micronutrients, including natural and synthetic folate (27). Due to the greater bioavailability of synthetic folate, we calculated dietary folate equivalents (DFE) as naturally occurring food folate + (1.7 × synthetic folate) (28). FA is found in a variety of foods (29, 30), and some correlation with other nutrients is expected (31); however, dietary patterns do not fully explain variance in FA intake (32). Therefore, examination of dietary FA intake among nonsupplementers can serve as a proxy for the independent effect of FA. Accordingly, we categorized participants into 1 of 3 exclusive groups: any FA-containing supplement use during periconception, no FA-containing supplement use but met the US recommendations for women of childbearing potential (28) based on estimated dietary intake (i.e., DFE ≥400 μg/d), and no FA-containing supplement use and low estimated dietary intake (i.e., DFE <400 μg/d).

We considered an array of potential confounders based on a priori knowledge of associations with interpregnancy interval and at least 1 malformation under study. These factors included maternal and paternal sociodemographic characteristics (study center, age at the prior delivery, race/ethnicity, US born, years of education, and annual household income), reproductive and pregnancy history (gravidity, use of fertility treatment, pregnancy intention, and use of birth control from 3 mo before pregnancy), and health-related behaviors (smoking or alcohol use from 1 mo before through 3 mo into pregnancy). We used a change-in-estimate approach to determine which potential confounding factors we would include in the multivariable regression models (33). Specifically, the set of covariates were those that when added to the model resulted in ≥10% change in the OR estimate for ≥1 defect under study. These factors were study center, maternal age, maternal race/ethnicity, pregnancy intention, and annual household income.

Our analysis included a subset of NBDPS participants with ≥1 previous pregnancy, whose interpregnancy interval was <24 mo, and whose preceding pregnancy resulted in a singleton live birth. We required that the prior pregnancy resulted in live birth because the pregnancy must have lasted long enough for depletion to take effect (34), and live births generally occur after 20 weeks of gestation. Fetal loss after 20 weeks of gestation is speculated to be a confounder (35) because it tends to be associated with shorter interpregnancy intervals (36) and may share underlying etiology with some defects (37). We included isolated cases (affected by only 1 malformation) for defect groups with ≥100 in total and ≥10 in each interpregnancy interval category. We included any defect group meeting these criteria, not just those known to be related to FA, because *1*) we aimed to assess short interval associations with birth defects in general, as well as jointly with FA; *2*) it is not well established which defects are FA dependent; and *3*) non-FA-dependent defects may be affected by other nutrients, such as those co-occurring in multivitamins. For cardiac defects, we included only simple cases (discrete anatomically). We did not consider cardiac conditions that generally are explained by premature delivery or are misclassified (e.g., atrial septal defects) (38), although given the rigorous classification procedures, it is unlikely that such defects would be included in the NBDPS (39). Furthermore, we excluded participants with extreme estimated daily caloric intake (<500 or >3800) or missing information on outcome of the preceding pregnancy, diet, supplement use, or maternal characteristics. We did allow for missing data on income (e.g., refusals to disclose), paternal characteristics, and pregnancy intention using unknown/refused categories.

We used unconditional logistic regression models with Firth's penalized likelihood (40) to estimate ORs and profile likelihood CIs, adjusted for the aforementioned covariates. Firth's penalized likelihood is an alternative estimation approach for rare outcomes (40). We estimated malformation-specific associations with interpregnancy interval (<6, 6–11, and 12–17 mo compared with 18–23 mo) and with FA intake (DFE <400 and ≥400 μg/d among non-FA supplementers compared with any FA supplement use). Following, we evaluated joint effects by estimating ORs for exclusive joint categorizations of these 2 exposures: <6-mo intervals + no FA supplement use and DFE <400 μg/d, <6-mo intervals + no FA supplement use and DFE ≥400 μg/d, <6-mo intervals + any FA supplement use, 6- to 23-mo intervals + no FA supplement use and DFE <400 μg/d, 6- to 23-mo intervals + no FA supplement use and DFE ≥400 μg/d, and 6- to 23-mo intervals + any FA supplement use (reference). We dichotomized at 6 mo because the starkest associations have been observed for <6-mo intervals in other studies (3, 4, 6, 23).

We adjusted for multiple comparisons using the Bonferroni and Dunn method (41, 42) by dividing the original α by the number of comparisons. In our analysis of joint effects of interval length and FA, there are 5 comparisons, so we reported 99% CIs. Although we made this adjustment, we did not accept or reject our hypotheses based on a specific statistical significance threshold, as now advised by the American Statistical Association (43). Rather, we focused on the strength of the association, where we considered ≥20% relative increase (OR > 1.2) or decrease (OR < 0.8) in odds to represent a potentially meaningful association, as well as consistency with prior research and plausibility (44). We also considered precision; however, we did not consider a result to provide evidence only if the 99% confidence bounds excluded 1 because this would be analogous to only accepting results meeting a statistical significance threshold (45). We were cognizant that by evaluating each defect in isolation, the number of exposed cases would be small, leading to imprecise estimates. However, we believed it was important to conduct each analysis by defect group. Had we instead combined all defects, the result might have been a mixture of heterogeneous estimates that could mask effects that only occur among certain defects. We did not report estimates if there was only 1 exposed case or if the model did not converge. We conducted analyses using SAS/STAT software version 9.4 for Windows (SAS Institute) (46).

Results

Of the 32,187 cases and 11,814 controls enrolled in the NBDPS, 3219 cases and 2508 controls met the eligibility criteria for our analyses. The primary exclusion reasons were no prior pregnancies, prior interpregnancy interval ≥24 mo, and prior pregnancy ending in miscarriage (**Figure 1**). The isolated noncardiac defects included anencephaly and craniorachischisis (n = 137), spina bifida (n = 268), cleft palate (n = 261), cleft lip (with or without cleft palate) (n = 599), diaphragmatic hernia (n = 138), hypospadias (second/third degree) (males only, n = 339), craniosynostosis (n = 349), and gastroschisis (n = 154). The simple cardiac defects included tetralogy of Fallot (173), dextro-rotated transposition of the great arteries (d-TGA) (n = 127), coarctation of the aorta (n = 115), hypoplastic left heart syndrome (HLHS) (n = 134), pulmonary valve stenosis (PVS) (n = 251), and ventricular septal defect (VSD, perimembranous) (n = 174).

A slightly higher proportion of cases were non-Hispanic white, primiparous (prior to the study pregnancy), unintended pregnancies, and smokers (**Table 1**). There were slight variations in age and income. Cases and controls were similar with respect to the other characteristics. Differences were more notable among the controls by interpregnancy interval. Mothers with intervals of <6 mo tended to be <25 years old at the prior delivery, whereas women with interpregnancy intervals of ≥6 mo were older. A higher proportion of women with shorter interpregnancy intervals self-identified as black or Hispanic, had lower educational attainment and lower income, had ≥2 prior pregnancies, reported the study pregnancy as unintended, and were smokers. Women with short intervals were also less likely to be born in the United States, use fertility treatment, and be drinkers. Similar patterns were exhibited among the controls who reported no FA supplement use (see Table 1). For all groupings, there were also variations by study center.

A higher proportion of controls with shorter intervals reported no periconceptional FA supplement use compared with controls with longer intervals (29.7%, 29.5%, 22.8%, and 22.2% for <6, 6–11, 12–17, and 18–23 mo, respectively). As seen in other studies (47), these differences appeared to be explained by other socioeconomic factors because the association between interpregnancy interval and supplement use was null upon adjustment for confounders. Among non-FA supplementers, there were no appreciable differences between interval and dietary FA intake (data not shown).

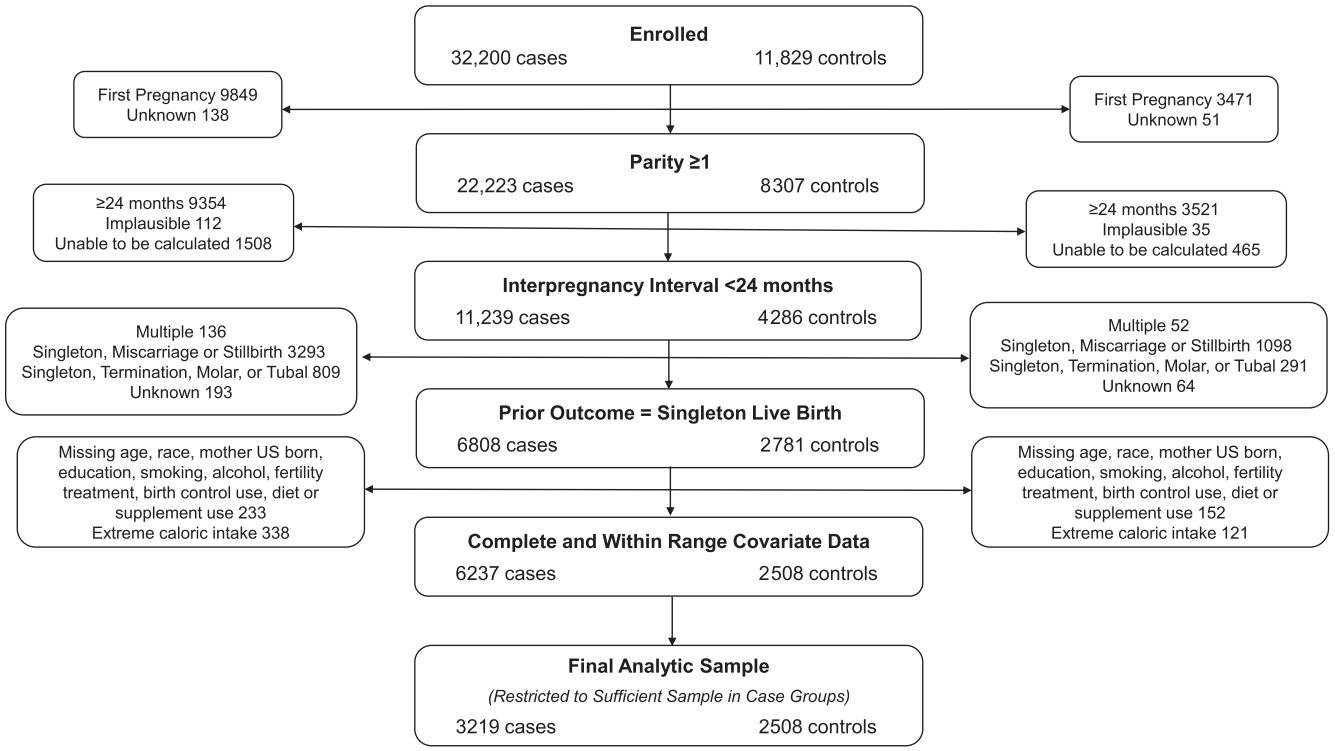

FIGURE 1 Eligibility flowchart.

A higher proportion of cases compared with controls had interpregnancy intervals of <6 mo (11.8% compared with 9.9% respectively). We observed positive associations with intervals of <6 mo, compared with 18–23 mo, for 4/8 noncardiac and 3/6 cardiac malformations studied (**Table 2**). The most notable increases were observed for gastroschisis (OR: 2.3; 99% CI: 1.1, 4.7), PVS (OR: 1.7; 99% CI: 0.92, 3.2), d-TGA (OR: 1.7; 99% CI: 0.69, 4.0), and craniosynostosis (OR: 1.5; 99% CI: 0.86, 2.6). Positive associations were also observed with 6–11 mo for gastroschisis and PVS and with 12–17 mo for PVS and d-TGA. An inverse association was observed with anencephaly with 6- to 11-mo intervals.

A higher proportion of cases compared with controls did not supplement with FA and had estimated DFE <400 μg/d (11.6% compared with 9.3%, respectively). We observed positive associations with no FA supplement use and DFE <400 μg/d, compared with any FA supplement use, for 5/8 noncardiac and 4/6 cardiac defects (**Table 3**). The strongest associations were observed for d-TGA (OR: 1.7; 99% CI: 0.77, 3.5), cleft palate (OR: 1.6; 99% CI: 0.93, 2.6), PVS (OR: 1.6; 99% CI: 0.90, 2.6), and spina bifida (OR: 1.5; 99% CI: 0.91, 2.5). Although estimates were imprecise, adjusted ORs for no FA supplement use and DFE ≥400 μg/d, compared with any FA supplement use, were >1.2 for 1/8 noncardiac and 3/6 cardiac defects; conversely, inverse associations were observed for 1/8 noncardiac and 1/6 cardiac defects.

Our assessment of the joint effects of interval length and FA intake was hindered by imprecision and small numbers of jointly exposed cases. Still, we noted some general patterns (**Figure 2**). Among participants who supplemented with FA, ORs comparing intervals of <6 mo to 6–23 mo were <1.2 for 6/8 cardiac defects [anencephaly (OR: 0.73; 99% CI: 0.25, 1.7), hypospadias (OR: 0.74; 99% CI: 0.34, 1.4), spina bifida (OR: 0.96; 99% CI: 0.46, 1.8), diaphragmatic hernia (OR: 1.1; 99% CI: 0.41, 2.4), craniosynostosis (OR: 1.1; 99% CI: 0.59, 2.0), and cleft palate (OR: 1.1; 99% CI: 0.57, 2.1)] and 3/6 cardiac defects [coarctation of the aorta (OR: 0.95; 99% CI: 0.30, 2.4), tetralogy of Fallot (OR: 1.0; 99% CI: 0.41, 2.3), and VSD (OR: 1.1; 99% CI; 0.48, 2.3)]; estimates were >1.2 for the other 2/8 noncardiac defects [cleft lip (OR: 1.3; 99% CI: 0.84, 2.0) and gastroschisis (OR: 1.3; 99% CI: 0.52, 2.7)] and 3/6 cardiac defects [PVS (OR: 1.4; 99% CI: 0.74, 2.5), d-TGA (OR: 1.4; 99% CI: 0.51, 3.1), and HLHS (OR: 1.3; 99% CI: 0.50, 3.0)]. In contrast, with intervals of <6 mo + no FA supplement use and DFE <400 μg/d, ORs were >1.2 for 6/8 noncardiac defects [gastroschisis (OR: 3.4; 99% CI: 0.93, 10.1), hypospadias (OR: 3.3; 99% CI: 0.93, 9.7), craniosynostosis (OR: 3.1; 99% CI: 0.89, 8.9), anencephaly (OR: 2.4; 99% CI: 0.47, 8.2), cleft palate (OR: 2.0; 99% CI: 0.48, 6.4), and cleft lip (OR: 1.8; 99% CI: 0.66, 4.4)] and 4/6 cardiac defects [coarctation of the aorta (OR: 3.3; 99% CI: 0.51, 13.1), tetralogy of Fallot (OR: 3.3; 99% CI: 0.77, 10.7), PVS (OR: 2.5; 99% CI: 0.65, 7.5), and VSD (OR: 1.3; 99% CI: 0.13, 5.6)]. With intervals <6 mo + no FA supplement use and DFE ≥400 μg/d, OR estimates were comparatively lower but still >1.2 for 6/8 noncardiac defects [craniosynostosis (OR: 2.6; 99% CI: 0.88, 6.5), gastroschisis (OR: 2.2; 99% CI: 0.72, 5.7), cleft lip (OR: 1.8; 99% CI: 0.84, 3.5), diaphragmatic hernia (OR: 1.7; 99% CI: 0.34, 5.6), cleft palate (OR: 1.4; 99% CI: 0.38, 3.9), and spina bifida (OR: 1.3; 99% CI: 0.40, 3.5)] and 3/6 cardiac defects [d-TGA (OR: 2.8; 99% CI: 0.7, 8.7), tetralogy of Fallot (OR: 2.1; 99% CI: 0.57, 6.1), and coarctation of the aorta (OR: 1.3; 99% CI: 0.14, 5.8)].

TABLE 1 Maternal characteristics by case–control status, interpregnancy interval, and folic acid intake, National Birth Defect Prevention Study (United States, 1997–2011)[1]

				Interpregnancy interval (controls)				Folic acid intake (controls)		
								No FA supplement use (B1–P2)		Any FA supplement use (B1–P2)
		Cases[2]	Controls	<6 mo	6–11 mo	12–17 mo	18–23 mo	DFE <400 μg	DFE ≥400 μg	
	n	3219	2508	249	681	842	736	233	397	1878
Maternal age at prior delivery, %										
<20 y	%	13.6	14.2	16.9	16.0	13.3	12.5	24.0	28.2	10.0
20–24 y	%	28.1	26.8	37.8	27.3	25.1	24.6	35.6	32.5	24.5
25–29 y	%	29.5	31.9	24.5	30.7	32.5	34.7	20.2	25.2	34.7
≥30 y	%	28.9	27.2	20.9	26.0	29.1	28.3	20.2	14.1	30.8
Paternal age at prior delivery, %										
<20 y	%	5.5	5.9	8.8	7.3	5.0	4.6	10.7	10.6	4.3
20–24 y	%	21.4	21.4	27.3	23.4	20.4	18.6	31.8	28.5	18.6
25–29 y	%	29.0	28.2	25.7	26.7	29.0	29.6	22.8	24.9	29.6
≥30 y	%	41.3	41.8	35.3	40.2	42.4	44.8	29.2	29.0	46.1
Unknown/refused	%	2.8	2.7	2.8	2.4	3.2	2.3	5.6	7.1	1.4
Maternal race/ethnicity, %										
Non-Hispanic white	%	66.8	63.6	47.4	58.3	70.4	66.3	42.9	38.8	71.5
Non-Hispanic black	%	6.2	8.6	15.3	11.0	5.3	7.9	19.3	14.4	6.1
Hispanic	%	20.6	22.1	32.9	25.1	19.1	19.2	32.2	41.1	16.9
Other	%	6.3	5.6	4.4	5.6	5.1	6.7	5.6	5.8	5.6
Paternal race/ethnicity, %										
Non-Hispanic white	%	63.8	61.7	45.4	54.8	68.4	65.9	40.3	36.0	69.8
Non-Hispanic black	%	8.0	9.9	18.1	12.6	6.1	8.8	20.2	15.1	7.5
Hispanic	%	21.8	22.1	31.3	25.6	19.7	18.6	32.2	41.1	16.9
Other	%	5.4	5.3	3.2	6.0	4.4	6.3	5.6	6.6	5.0
Unknown/refused	%	1.1	1.1	2.0	1.0	1.4	0.4	1.7	1.3	1.0
Mother US born, %										
Yes	%	83.6	81.8	79.5	80.3	82.8	82.9	78.1	70.0	84.8
No	%	16.4	18.2	20.5	19.7	17.2	17.1	21.9	30.0	15.2
Father US born, %										
Yes	%	81.0	79.8	74.7	78.4	81.2	81.3	75.5	61.7	84.2
No	%	18.4	19.5	24.5	21.0	17.7	18.5	22.8	36.8	15.4
Unknown/refused	%	0.6	0.7	0.8	0.6	1.1	0.3	1.7	1.5	0.4
Maternal education, y										
<12	%	17.1	16.4	26.9	17.9	14.3	13.7	29.2	35.3	10.8
12	%	23.0	23.7	32.1	25.7	20.9	22.2	32.6	32.8	20.7
>12	%	59.9	60.0	41.0	56.4	64.9	64.1	38.2	32.0	68.6
Paternal education, y										
<12	%	16.2	15.4	23.7	17.6	13.7	12.6	25.3	30.7	11.0
12	%	27.4	26.9	35.3	28.9	23.8	25.8	35.2	31.0	25.0
>12	%	54.0	55.2	37.4	51.1	59.6	60.1	33.5	33.3	62.6
Unknown/refused	%	2.5	2.4	3.6	2.4	3.0	1.5	6.0	5.0	1.4

(*Continued*)

TABLE 1 (*Continued*)

				Interpregnancy interval (controls)				Folic acid intake (controls)		
								No FA supplement use (B1–P2)		Any FA supplement use (B1–P2)
		Cases[2]	Controls	<6 mo	6–11 mo	12–17 mo	18–23 mo	DFE <400 μg	DFE ≥400 μg	
Annual household income, %										
<$10,000	%	17.6	17.6	29.3	21.4	14.9	13.3	31.3	35.5	12.1
$10,000–$50,000	%	43.9	43.3	42.2	43.5	42.9	43.9	46.8	46.1	42.2
>$50,000	%	34.7	35.5	22.1	31.0	39.2	39.8	17.2	12.9	42.5
Unknown/refused	%	3.9	3.7	6.4	4.1	3.1	3.0	4.7	5.5	3.1
Gravidity, %										
1	%	43.0	41.6	36.6	39.7	43.5	43.1	34.3	37.0	43.5
≥2	%	57.0	58.4	63.5	60.4	56.5	56.9	65.7	63.0	56.5
Fertility treatment, %										
Yes	%	2.3	2.1	0.0	1.8	2.6	2.5	0.9	0.8	2.5
No	%	97.7	97.9	100.0	98.2	97.4	97.6	99.1	99.2	97.5
Pregnancy intention, %										
Intended	%	39.3	39.7	16.9	17.8	21.3	22.0	31.8	26.5	43.5
Unintended/ambivalent	%	41.5	40.2	59.4	50.7	35.6	29.2	54.1	56.2	35.1
Unknown/refused	%	19.2	20.1	23.7	31.6	43.1	48.8	14.2	17.4	21.4
Any birth control (B3–), %										
Yes	%	30.1	31.4	29.7	31.3	32.4	30.8	25.8	28.5	32.7
No	%	69.9	68.6	70.3	68.7	67.6	69.2	74.3	71.5	67.3
Smoking (B1–P3), %										
Yes	%	16.1	14.9	20.5	16.7	13.7	12.8	18.9	20.2	13.3
No	%	83.9	85.1	79.5	83.3	86.3	87.2	81.1	79.9	86.7
Alcohol use (B1–P3), %										
Yes	%	31.5	31.4	25.3	32.5	31.8	31.9	30.0	24.7	33.0
No	%	68.5	68.6	74.7	67.6	68.2	68.1	70.0	75.3	67.0
Study center location, %										
Arkansas	%	12.8	11.3	16.9	11.9	10.1	10.3	9.4	11.6	11.5
California	%	12.2	10.1	10.8	10.7	10.0	9.2	12.5	14.9	8.7
Iowa	%	10.9	12.3	8.4	12.3	13.1	12.6	9.0	9.6	13.3
Massachusetts	%	12.0	11.0	8.4	12.0	10.6	11.3	9.0	5.3	12.4
New Jersey	%	4.4	4.0	4.4	5.0	3.6	3.5	3.0	4.0	4.2
New York	%	7.8	8.7	6.8	8.2	9.1	9.4	9.0	8.1	8.8
Texas	%	8.6	10.6	16.9	11.6	9.4	9.0	13.3	18.4	8.6
CDC/Atlanta	%	9.4	9.5	11.7	10.4	8.6	9.0	12.5	11.3	8.7
North Carolina	%	7.4	7.9	10.0	7.5	7.5	7.9	9.4	7.3	7.8
Utah	%	14.4	14.7	5.6	10.3	18.2	17.8	12.9	9.6	16.0

[1]B1–P2, 1 mo before pregnancy through the first 2 mo of pregnancy; B1–P3, 1 mo before pregnancy through the first 3 mo of pregnancy; B3–, any time since 3 mo prior to pregnancy; FA, folic acid.

[2]Cases include isolated noncardiac defects: anencephaly and craniorachischisis ($n = 137$), spina bifida ($n = 268$), cleft palate ($n = 261$), cleft lip (with or without cleft palate) ($n = 599$), diaphragmatic hernia ($n = 138$), hypospadias (second/third degree) (males only, $n = 339$), craniosynostosis ($n = 349$), and gastroschisis ($n = 154$); and simple cardiac defects: tetralogy of Fallot (173), dextro-rotated transposition of the great arteries ($n = 127$), coarctation of the aorta ($n = 115$), hypoplastic left heart syndrome ($n = 134$), pulmonary valve stenosis ($n = 251$), and ventricular septal defect (perimembranous) ($n = 174$).

TABLE 2 Associations between interpregnancy interval categories and isolated birth defects, National Birth Defect Prevention Study (United States, 1997–2011)[1]

		Interpregnancy interval			
		<6 mo	6–11 mo	12–17 mo	18–23 mo
Noncardiac defects					
Anencephaly/craniorachischisis	*n*	14	32	45	46
	aOR (99% CI)	0.80 (0.33, 1.8)	0.71 (0.38, 1.3)	0.85 (0.48, 1.5)	1.00
Spina bifida	*n*	26	74	86	82
	aOR (99% CI)	0.84 (0.44, 1.5)	0.89 (0.57, 1.4)	0.89 (0.58, 1.4)	1.00
Cleft palate	n	31	71	90	69
	aOR (99% CI)	1.3 (0.69, 2.3)	1.1 (0.67, 1.7)	1.1 (0.72, 1.7)	1.00
Cleft lip (w/wo cleft palate)	*n*	84	152	188	175
	aOR (99% CI)	1.4 (0.91, 2.1)	0.92 (0.66, 1.3)	0.91 (0.68, 1.2)	1.00
Diaphragmatic hernia	*n*	14	38	50	36
	aOR (99% CI)	1.1 (0.43, 2.4)	1.1 (0.58, 2.0)	1.2 (0.67, 2.1)	1.00
Hypospadias second/third degree	*n*	29	81	127	102
	aOR (99% CI)	1.0 (0.55, 1.8)	0.92 (0.60, 1.4)	1.1 (0.74, 1.6)	1.00
Craniosynostosis	*n*	39	81	127	102
	aOR (99% CI)	1.5 (0.86, 2.6)	0.97 (0.63, 1.5)	1.1 (0.73, 1.5)	1.00
Gastroschisis	*n*	29	56	38	31
	aOR (99% CI)	2.3 (1.1, 4.7)	1.8 (0.98, 3.4)	1.0 (0.55, 2.0)	1.00
Cardiac defects					
Tetralogy of Fallot	*n*	22	51	50	50
	aOR (99% CI)	1.3 (0.64, 2.7)	1.1 (0.65, 1.9)	0.88 (0.52, 1.5)	1.00
d-Transposition of the great arteries	*n*	15	30	55	27
	aOR (99% CI)	1.7 (0.69, 4.0)	1.2 (0.58, 2.4)	1.7 (0.95, 3.3)	1.00
Coarctation of the aorta	*n*	12	28	42	33
	aOR (99% CI)	1.1 (0.41, 2.6)	0.89 (0.44, 1.8)	1.1 (0.58, 2.0)	1.00
Hypoplastic left heart syndrome	*n*	10	33	53	38
	aOR (99% CI)	1.1 (0.38, 2.6)	1.1 (0.59, 2.1)	1.2 (0.69, 2.1)	1.00
Pulmonary valve stenosis	*n*	34	78	85	54
	aOR (99% CI)	1.7 (0.92, 3.2)	1.5 (0.95, 2.5)	1.4 (0.86, 2.2)	1.00
VSD perimembranous	*n*	20	57	51	46
	aOR (99% CI)	1.1 (0.52, 2.3)	1.2 (0.72, 2.1)	0.97 (0.56, 1.7)	1.00

[1] Adjusted OR estimated from multivariable logistic regression with Firth's penalized likelihood with 99% profile likelihood CIs, controlling for maternal age at the prior delivery, maternal race/ethnicity, annual household income, pregnancy intention, and study center. aOR, adjusted OR; VSD, ventricular septal defect; w/wo, with and without.

Discussion

In this multisite, population-based case–control study, we found a trend of associations between short interpregnancy intervals and several malformations. To our knowledge, our study provides the first empirical evidence to suggest that nutritional depletion may be a part of the underlying biologic mechanism (**Figure 3**). For most defects, short intervals were not associated with increased risks among FA supplementers. The strongest associations with short intervals, although imprecise, were observed among women who did not supplement and had DFE <400 μg/d. We were not able to explore other specific nutrients and several of the defects have not previously been associated with FA, raising the possibility that the mechanism may not be attributed to FA specifically. However, the fact that short intervals were not associated with increased risks for most defects among women who took supplements, many of which presumably contained multiple nutrients, while nonsupplementers with low dietary folate exhibited increased risks, points to FA being a possible underlying factor for certain defects.

Prior literature suggests a possible role of FA in the interpregnancy interval mechanism (8, 10) and birth defect etiology (48–51). Randomized controlled trials and observational studies have conclusively shown daily FA supplement use more than halves NTD risk (48). Although less conclusive, meta-analyses suggest modest protective effects for cleft palate (RR: 0.7; 95% CI: 0.1, 10.9), cleft lip (RR: 0.8; 95% CI: 0.1, 4.4), and cardiovascular defects (RR: 0.6; 95% CI: 0.2, 1.3) (48), which are further supported by pre- and post-FA fortification studies (49, 51) and have led some to consider these defects as "folate sensitive" (52). At least 1 study has reported reduced risk for gastroschisis with sustained FA supplement use in the first trimester (OR: 0.3; 95% CI: 0.1, 0.7) (50). Similarly, we observed associations with DFE <400 μg among nonsupplementers, compared with any FA supplement use, for spina bifida, clefts, gastroschisis, and 4/6 of the heart defects; our observed association with craniosynostosis has not been previously reported.

A challenge in observational study of any isolated nutrient is its potential correlation with other nutrients (31). We cannot rule out the possibility that associations may be explained by other nutrients, the specifics of which may vary for a given defect. For instance, research suggests that 1-carbon micronutrients (e.g., B-6, choline, and methionine), alone or in combination with FA, may decrease risks for NTDs (53) and defects not typically associated with FA, including hypospadias (54) and craniosynostosis (55). Higher quality diets (e.g., those

TABLE 3 Associations between FA intake and isolated birth defects, National Birth Defect Prevention Study (United States, 1997–2011)[1]

		FA Intake		
		DFE <400 μg and no FA supplement use	DFE ≥400 μg and no FA supplement use	Any FA supplement use (B1–P2)
Noncardiac defects				
Anencephaly/craniorachischisis	*n*	16	16	105
	aOR (99% CI)	1.2 (0.53, 2.4)	0.64 (0.29, 1.3)	1.00
Spina bifida	*n*	40	39	189
	aOR (99% CI)	1.5 (0.91, 2.5)	0.82 (0.49, 1.3)	1.00
Cleft palate	*n*	36	35	190
	aOR (99% CI)	1.6 (0.93, 2.6)	0.92 (0.53, 1.5)	1.00
Cleft lip (w/wo cleft palate)	*n*	70	101	428
	aOR (99% CI)	1.3 (0.90, 2.0)	1.1 (0.74, 1.5)	1.00
Diaphragmatic hernia	*n*	12	29	97
	aOR (99% CI)	1.1 (0.43, 2.3)	1.4 (0.77, 2.6)	1.00
Hypospadias second/third degree	*n*	28	35	276
	aOR (99% CI)	1.1 (0.61, 1.9)	0.89 (0.52, 1.5)	1.00
Craniosynostosis	*n*	32	39	278
	aOR (99% CI)	1.3 (0.73, 2.1)	0.97 (0.59, 1.6)	1.00
Gastroschisis	*n*	26	36	92
	aOR (99% CI)	1.4 (0.74, 2.7)	1.1 (0.62, 1.9)	1.00
Cardiac defects				
Tetralogy of Fallot	*n*	21	29	123
	aOR (99% CI)	1.5 (0.73, 2.7)	1.3 (0.69, 2.2)	1.00
d-Transposition of the great arteries	*n*	16	21	90
	aOR (99% CI)	1.7 (0.77, 3.5)	1.4 (0.66, 2.6)	1.00
Coarctation of the aorta	*n*	11	19	85
	aOR (99% CI)	1.2 (0.47, 2.7)	1.3 (0.63, 2.6)	1.00
Hypoplastic left heart syndrome	*n*	13	14	107
	aOR (99% CI)	1.1 (0.48, 2.4)	0.78 (0.34, 1.6)	1.00
Pulmonary valve stenosis	*n*	35	34	182
	aOR (99% CI)	1.6 (0.90, 2.6)	0.92 (0.53, 1.5)	1.00
VSD perimembranous	*n*	18	31	125
	aOR (99% CI)	1.1 (0.54, 2.2)	1.1 (0.62, 1.9)	1.00

[1]Adjusted OR estimated from multivariable logistic regression with Firth's penalized likelihood with 99% profile likelihood CIs, controlling for maternal age at the prior delivery, maternal race/ethnicity, annual household income, pregnancy intention, and study center. aOR, adjusted OR; B1–P2, 1 mo before pregnancy through the first 2 mo of pregnancy; FA, folic acid; VSD, ventricular septal defect; w/wo, with and without.

containing more fruits and vegetables) have been found to decrease risks for a variety of defects [e.g., anencephaly, tetralogy of Fallot, craniosynostosis, cleft lip (56), hypospadias (57), and gastroschisis (50)]. Future research should explore this complexity to clarify each defect-specific mechanism.

In a retrospective Canadian cohort (1999–2007), Chen et al. (3) found that short intervals were more strongly associated with defects they defined as "folate-independent" (OR: 1.9; 95% CI: 1.1, 3.2) compared with "folate-dependent" defects [i.e., NTDs, clefts, cardiac defects, urinary tract defects, and limb defects (OR: 1.2; 95% CI: 0.9, 1.6)]. Similarly, we also found associations with a couple of defects not typically linked to FA. The largest limitation of Chen et al.'s study was that they did not have data on supplement use or diet (3). Our NTD associations did not manifest until we also accounted for FA intake. A prior NBDPS study found no difference in associations between <12-mo intervals and gastroschisis among women who supplemented with a multivitamin compared with those who did not; however, that former analysis did not consider diet (5). This is an important distinction, particularly in the age of fortification (58, 59).

Our design addresses certain limitations of prior research. The efficiency gained by sampling controls from the population base afforded us resources to capture detailed FA information from supplements and diet and relatively large numbers of specific defects with rigorous case classification. Still, several malformations were too rare to be examined. Although trends appeared fairly consistent across various defects, our estimates were imprecise. Some findings may have been due to chance, which may explain, for instance, the inverse associations observed with anencephaly. We were able to adjust for a number of covariates, although residual confounding cannot be entirely dismissed. We did not control for family history of defects, illicit drug use, or certain medications (e.g., antiepileptic drugs) because they tend to be rare (60–62) and are not known to be strongly related to interpregnancy interval (35). We chose not to adjust for BMI at the start of the study pregnancy, a risk factor for several birth defects (63), because the interpregnancy interval length correlates with changes in BMI between pregnancies (64, 65). BMI and breastfeeding should be examined in future research because it is not known the degree to which these factors may confound or modify the relations under study. We relied on

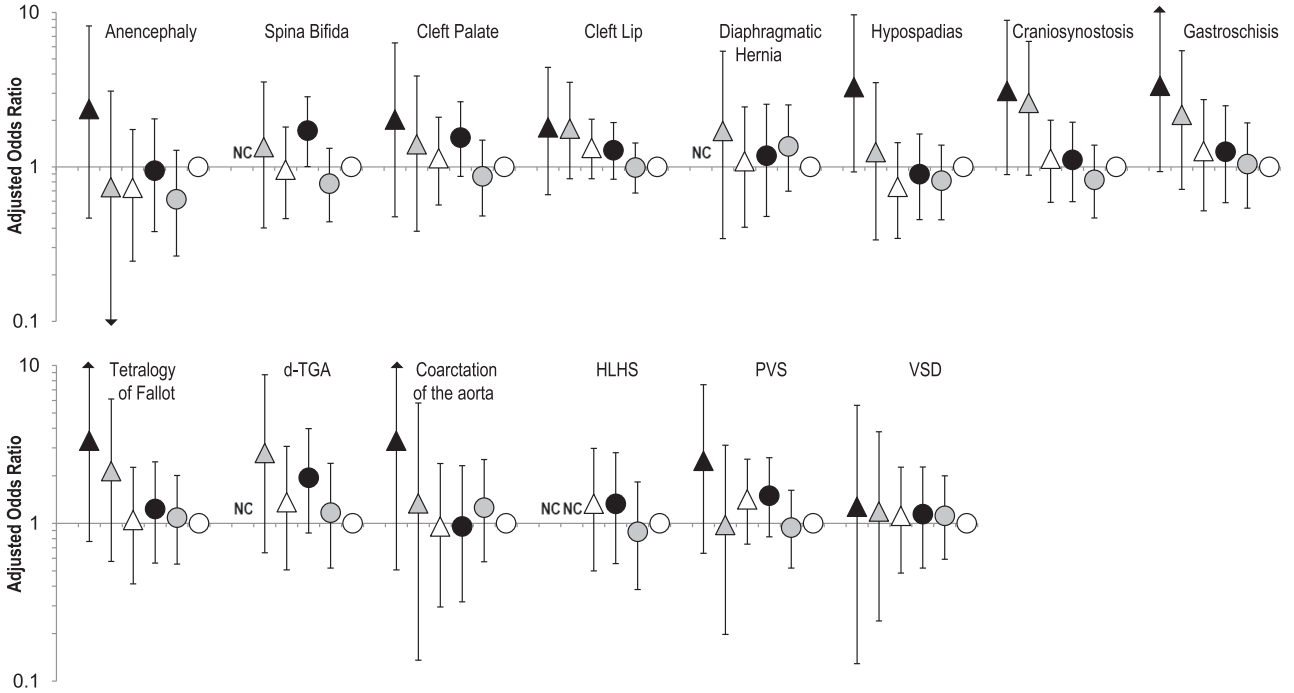

FIGURE 2 Forest plot of joint associations between short interpregnancy intervals of <6 mo + no FA supplement use and DFE <400 μg (black triangles), <6 mo + no FA supplement use and DFE ≥400 μg (gray triangles), <6 mo + any FA supplementation (white triangles), 6–23 mo + no FA supplement use and DFE <400 μg (black circles), 6–23 mo + no FA supplement use and DFE ≥400 μg (gray circles), and 6–23 mo + any FA supplement use (white circles) (reference group) with risks for select isolated birth defects. ORs (shapes) and 99% profile likelihood CIs (error bars) were computed from multivariable logistic regression models, with Firth's penalized likelihood, controlling for maternal age at the prior delivery, maternal race/ethnicity, annual household income, pregnancy intention, and study center. Cases include isolated noncardiac defects: anencephaly and craniorachischisis ($n = 137$), spina bifida ($n = 268$), cleft palate ($n = 261$), cleft lip (with or without cleft palate) ($n = 599$), diaphragmatic hernia ($n = 138$), hypospadias (second/third degree) (males only, $n = 339$), craniosynostosis ($n = 349$), and gastroschisis ($n = 154$); and simple cardiac defects: tetralogy of Fallot (173), d-TGA ($n = 127$), coarctation of the aorta ($n = 115$), HLHS ($n = 134$), PVS ($n = 251$), and VSD (perimembranous) ($n = 174$). Controls were nonmalformed live-borns ($n = 2508$). d-TGA, dextro-rotated transposition of the great arteries; DFE, dietary folate equivalents; FA, folic acid; HLHS, hypoplastic left heart syndrome; NC, not calculated; PVS, pulmonary valve stenosis; VSD, ventricular septal defect.

maternal recall up to 2 y after the study pregnancy. Although the Willett FFQ has been validated (26), the added questions on cereal intake have not. For these reasons, errors in DFE estimates may have occurred. However, because many people lack knowledge about specific nutritional content of food (66), we do not believe this misclassification would be differential with respect to case status. Prior research of recall bias in relation to nutrition and breast cancer has supported this speculation

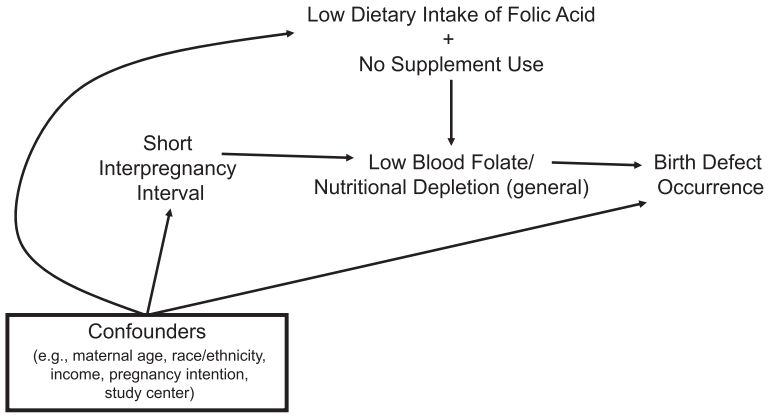

FIGURE 3 Conceptual model for nutrition/folate depletion as an explanation for the association between short interpregnancy intervals and increased risks for birth defects. Nutrient (folate) concentrations naturally decrease during pregnancy and postpartum. Under this paradigm, short interpregnancy intervals increase the risk for low blood folate (and nutritional depletion in general) at the start of the next pregnancy. This deficit then increases the risk for birth defect occurrence. Social and reproductive factors are related to likelihood of rapid repeat pregnancy and risks for birth defects. Such factors are also associated with dietary intake and supplement use, which modify the short interval–birth defect pathway by directly altering maternal serum concentrations.

(67). There may be reporting errors in FA supplement use. We conjecture that women who were truly supplementers were unlikely to report being non-FA supplementers, corresponding with near-perfect specificity; however, women who did not actually supplement may have reported taking FA supplements given the recommendations (68), which would correspond with imperfect sensitivity and may be differential with respect to case status. Even large errors in recall may have only minor impact on case–control findings when the predominant errors are nondifferential (random) or relate to differential sensitivity (69), as we believe them to be in our study. Future researchers should investigate dose, frequency, and timing and, as previously noted, the distinct role of FA compared with other nutrients [e.g., iron (8)].

Our study adds to the growing literature indicating that closely spaced pregnancies are at increased susceptibility to adverse outcomes. Short intervals were associated with a trend to increased risks for certain malformations, notably in the absence of FA supplement use. These associations do not appear to be explained by social or reproductive factors, including pregnancy intention. As seen in other studies (70, 71), supplement use occurred less often among unintended pregnancies. This finding reinforces the current recommendation that all women of childbearing potential should consume 400 μg of FA daily (68), which can be achieved with regular intake of most multivitamins. Replication of our findings is needed. To provide greater insight into the etiology and generalizability, future research should include larger sample sizes; data to evaluate correlated nutrient intake and absorption, diet quality, breastfeeding, and interpregnancy BMI; and be performed in countries without FA fortification. Such evidence, if found, could suggest that defect risks and/or other adverse outcomes associated with short birth spacing may be lessened by support from multivitamins and/or supplemental FA.

This study represents a secondary use of the data, which were collected prior to the conception of the specific research question examined in this study. We thank Natalie Archer for her replication of the case–control counts and exposure and covariate distributions of this analysis, in accordance with the NBDPS/BD-STEPS data replication policy. We also thank the mothers who participated in this study and the clinical coordinators, without whom this research would not be possible.

The authors' responsibilities were as follows—JMP: analyzed the data and wrote the initial draft of the manuscript; MMY, KDG, MTA, and MMW: provided critical review and edits to the manuscript; and all authors: formulated the initial study question and analytic plan and read and approved the final manuscript. The authors report no conflicts of interest.

Data Availability

Data described in the manuscript, code book, and analytic code may be made available upon request. The process for accessing the data used in this study is described at https://www.cdc.gov/ncbddd/birthdefects/nbdps-public-access-procedures.html.

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